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## Mesial Temporal Sclerosis: Chickens and Eggs

A B S T R A C T & C O M M E N T A R Y

**Source:** Scott RC, et al. Magnetic resonance imaging findings within 5 days of status epilepticus in childhood. *Brain.* 2002;125:1951-1959.

MESIAL TEMPORAL SCLEROSIS (MTS) IS THE MOST COMMON pathology found in surgical series of patients undergoing temporal lobectomy for pharmacologically intractable focal epilepsy. In fact, MTS with its classic MRI features (hippocampal volume loss, increased T2 signal, and loss of internal architecture) is the best predictor of a seizure-free surgical outcome, provided that MTS is concordant with the pre-operative electrographic ictal localization data. A better understanding of the mechanisms leading to this neuropathological substrate for temporal lobe epilepsy should provide fundamental insights into the pathophysiology of epileptogenesis.

Scott and colleagues describe the subacute effects of childhood status epilepticus (SE) on the hippocampus. They evaluated 35 children within 5 days of presentation with status epilepticus. They analyzed quantitative measures (T2 relaxometry and hippocampal volumetry) of MRI pathology. They also stratified the analysis according to whether the patients had prolonged febrile convulsions (PFC, 21 subjects) or afebrile status epilepticus (ASE). Nineteen PFC and all 14 ASE patients had never experienced SE previously.

This study found that hippocampal volumes were increased in all PFC patients vs controls (age-matched children undergoing cranial MRI to evaluate nonepileptic conditions, $P = 0.004$) but not in ASE patients ($P = 1.0$). T2 relaxation times were significantly increased for both PFC and ASE relative to controls if the scans were obtained within 2 days of SE. Scott et al concluded that PFC leads to hippocampal edema acutely and propose that this clinical presentation may eventually lead to MTS.

### COMMENTARY

Gowers expressed the view that "seizures beget seizures." As demonstrated by Scott et al, a certain kind of seizure, ie, prolonged febrile convulsions, can beget acute edema in the hippocampus that

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## INSIDE

may presage MTS and medical intractability.

Scott et al of course have not resolved the fundamental question of whether PFCs reflect an underlying predisposition to MTS and epilepsy or whether PFCs per se damage the hippocampus. They, in fact, acknowledge that there are genetic factors underlying complicated febrile seizures. Furthermore, hippocampal atrophy has been observed in 57% of patients with familial temporal lobe epilepsy (*Neurology.* 2001;56:166-172). Unfortunately, Scott et al did not repeat MRIs even less than a year later that might have revealed early signs of MTS exclusively in patients who had hippocampal edema. Such data would have extended the results of Van Landingham and colleagues (*Ann Neurol.* 1998;43:413-426). Those investigators demonstrated MTS in 4 of 15 children who had PFC with focal or lateralizing ictal findings. Of these, 2 of 4 patients showed MTS following acute edema caused by PFC. Moreover, PFCs are not the only answer, as suggested by the findings of Theodore and associates (*Neurology.* 1999;52:132-136) that hippocampal volume is inversely related to epilepsy duration, in support of Gowers' dictum.

Other than the theoretical chicken-or-egg and nature-vs-nurture considerations, the implications of these data for the practicing pediatrician and pediatric neurologist are obvious: treat febrile convulsions aggressively and anticipate medical intractability and surgical referral early in children with a history of PFC. **—ANDY DEAN**

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# Syncope and the Thread of Consciousness

ABSTRACT & COMMENTARY

**Source:** Soteriades ES, et al. Incidence and prognosis of syncope. *N Engl J Med*. 2002;347:878-885.

SYNCOPE IS A COMPOUND WORD DERIVED FROM 2 Greek roots: the adverb syn meaning "at once" and the verb koptein meaning "to cut." Therefore, the term refers to the actions of the Three Fates of Greek Mythology who both spun out and cut short the thread of each person's life and consciousness. Fortunately in clinical practice syncope is a brief, sudden loss of consciousness, associated with the inability to maintain postural tone, followed by spontaneous recovery.

Although syncope is common, its epidemiology and prognosis have not been well described. Soteriades and colleagues, therefore, evaluated the incidence, causes, and prognosis of syncope among men and women taking part in the Framingham Heart Study (Kannel WB, et al. *Am J Epidemiol*. 1979;110:281-290).

They followed the participants, 3563 men and 4251 women, for an average of 17 years. A total of 822 (348 men and 474 women; mean age, 66 years) reported having had a syncopal episode. The incidence rate of a first report of syncope was 6.2 per 1000 person years. The incidence increased with age: there was a sharp rise at 70 years to 11.1 per 1000 person years, and at 80 years there was a further increase for men and women, respectively, to 16.9 and 19.5 per 1000 person years.

The causes identified most frequently in men and women, respectively, were: cardiac causes (13% and 7%), unknown cause (31% and 41%), TIA or stroke (4% in both), seizure (7% and 3%), vasovagal faint (20% and 22%), orthostatic hypotension (9% and 10%), medication (6% and 7%), and other causes (10% and 6%).

Seventy-eight percent of participants (570) reported only 1 syncopal episode, 23% (157) reported 1 or more. The risk of recurrence was especially high among those with cardiac syncope (multivariable-adjusted hazard

ratio = 30.3).

During a mean follow-up of 8.6 years, among 2181 subjects, there were 847 deaths from all causes, 263 myocardial infarcts (MI) or deaths from coronary artery disease, and 178 fatal or nonfatal strokes. The risk of death was increased by 31% among all participants with syncope and was doubled among those with cardiac syncope, as compared to subjects without syncope. Syncope of unknown cause and neurologic syncope including TIA and seizure were associated with an increased risk of death; neurologic syncope with a three-fold risk of stroke. Vasovagal syncope was not associated with an increased risk of death, MI, or stroke.

**COMMENTARY**

The merits of this study are that it was population-based and, therefore, free of selection bias, and that the period of follow-up was long. The finding that cardiac syncope was associated with an increased risk of death and cardiovascular events is consistent with previous studies (Kapoor WN. *Medicine*. 1990;69:160-175) and current cardiologic evaluation and treatment of such patients. Likewise the finding that vasovagal syncope, including orthostatic and medication-induced faints, had a benign prognosis is not surprising and is in accord with the general clinical experience.

Neurologists will have difficulty accepting the authors' classification of TIA and seizures as "neurologic syncope." Soteriades et al's statement that "the increased risk of stroke in participants with neurologic syncope may be attributable to preexisting cerebrovascular disease," reflects the fact that a TIA even by another name increased the risk for stroke. Therefore, when the thread of consciousness is cut, the means, whether by a simple faint, or by a TIA, matters. **—JOHN J. CARONNA**

# Coffee Drinking May be Associated with SAH

ABSTRACT & COMMENTARY

**Source:** Isaksen J, et al. Risk factors for aneurysmal subarachnoid hemorrhage: The tromso study. *J Neurol Neurosurg Psychiatry*. 2002;73:185-187.

Coffee, whether mocha cappuccino or dishwater swill, remains a staple of our diet, particularly among the overworked citizens of the medical community. Periodically, a dangerous epidemiological association emerges, such as a possible increased risk of pancreatic cancer, only to be debunked in further analysis. With a late night cup of joe in hand, we approach these new data.

Isaksen and associates studied individuals with aneurysmal subarachnoid hemorrhage (SAH) drawn from an overall study population of 52,792 in Tromso, Norway. There were 233 cases with SAH, however only 56 of these were confirmed by angiography or autopsy. A subset of the 56 had survey data taken prior to bleeding (n = 26) and were entered into final analysis. Each case was age and sex matched with 4 controls.

Systolic hypertension, cigarette smoking, and coffee intake were all associated with SAH. These factors remained significant in multivariate analysis with odds ratios of 2.46, 4.55, and 3.86 respectively. Coffee consumption was classified as either low ≤ 5 or high > 5 cups a day. High quantities of coffee were consumed by 85% of cases but only 60% of controls ($P = 0.004$). Any cigarette smoking proved harmful, with current cigarette use emerging as the most powerful risk factor.

**COMMENTARY**

While hypertension and smoking have been previously associated with SAH, this is the first report of a role for coffee consumption. The methodology of the study, however, begs several further questions. Was the coffee caffeinated or decaffeinated? Are other caffeinated beverages harmful? What was the temporal relationship between coffee intake and the occurrence of SAH; was this an immediate or delayed effect? Is this risk relationship linear (ie, dose dependent) or is it restricted to only excess coffee consumption? Does coffee lead to aneurysm formation or does it precipitate rupture of existing lesions?

These data thus provoke more questions than they solve. Given that an excess of anything is best to be avoided, one might advise our 6-cup-of-coffee/day drinkers as well as ourselves, to perhaps cut down by a few. **—ALAN Z. SEGAL**

# Treatment of Acute Stroke with Mechanical Clot Extraction

ABSTRACT & COMMENTARY

**Source:** Mayer TE, et al. Treatment of basilar artery embolism with a mechanical extraction device. *Stroke*. 2002;33:2232-2235.

Intravenous thrombolysis with tissue plasminogen activator (tPA) for acute stroke is limited by a

short time window (less than 3 hours) and may not be effective when the burden of clot is large. Local thrombolysis with tPA by an intra-arterial (IA) route may be more effective for large thrombi, particularly in the basilar artery or in the distal internal carotid or proximal middle cerebral artery. IA thrombolysis may also be used in a wider time window such as up to 6 hours in the anterior circulation or perhaps 12-24 hours for the basilar artery. Use of the IA route also offers the possibility of using mechanical devices, limiting the necessary dose of thrombolytic, or eliminating the need for chemical lysis entirely. Although hemorrhages may still complicate strokes treated with mechanical techniques, the overall risk of ICH is significantly attenuated.

A number of different mechanical devices have been piloted in animal and human studies—all involving modifications of microcatheters capable of being navigated into the intracranial vasculature. These technologies follow 2 basic strategies: clot destruction or clot removal. Thrombi may be destroyed by the inflation of angioplasty balloons or the use of devices such as endovascular lasers or "angiojet" (pulsation) systems. Alternatively, clots may be "snared" with baskets or other cathteter tips designed to trap and extract thrombi from occluded vessels. Such retrieval systems represent an important advance because unlike with tPA or mechanical clot disruption, there is no significant risk of dangerous distal embolism. In the case of a mid-basilar thrombosis, for instance, propagation of clot fragments distally to the basilar tip following tPA often puts the vital thalamoperforator vessels at risk. In the middle cerebral artery system, showering of clot material distally into small cortical branches may produce clinically significant infarcts. With clot extraction, such complications are largely avoided.

In an extremely preliminary report, Mayer and associates present data on 5 patients with basilar artery thromboses treated with a device called "Neuronet." This nitinol self-expanding basket, delivered with a microcatheter, is capable of "loading up" thrombus and retrieving it from an occluded vessel. Five total patients were studied. The first 2 failed, requiring "rescue" tPA administration. In the subsequent 3 cases (Patients 3-5), clot retrieval was facilitated by the inflation of balloons in the vertebral arteries proximal to the site of occlusion. This produced a reversal of flow and allowed the clot to be removed. Maintenance of anterograde flow toward the clot would otherwise "keep it in place like a cork." Patients 3 and 5 achieved TIMI III flow with the Neuronet, while patient 4 did require tPA to achieve optimal recanalization. This patient had a small amount of residual clot at the basilar tip despite a total of 3 attempts at retraction maneuvers. Overall, 3 out of 5 patients had good clinical outcomes with 2 remaining severely disabled. These clinical results would be considered superior to those seen among historical controls suffering from basilar thromboses.

**COMMENTARY**

This study, though limited, represents important pilot data. Mechanical clot retrieval appears to be safe and effective. Additional reports are sure to follow, including some from our own center. In conjunction with the interventional neuroradiology group at Cornell, our Stroke Service has been fortunate to participate in the MERCI, Concentric Retriever Trial. In Phase I, 29 patients have been treated with a nitinol helical coil designed to screw into thrombi and extract them in a manner similar to that used with "Neuronet." There were no device related complications in Phase I of MERCI and the Phase II study is currently in preparation. **—ALAN Z. SEGAL**

# Depression and Multiple Sclerosis: No Negative Effects of Beta-interferon

ABSTRACTS & COMMENTARY

**Sources:** Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. *Neurology.* 2002;59:674-678; Patten SB, Metz LM. Interferon-beta1a and depression in secondary progressive MS: Data from the SPECTRIMS Trial. *Neurology.* 2002;59:744-746; Feinstein A, et al. Multiple sclerosis, interferon-beta1b and depression. *J Neurol.* 2002;249: 815-820.

In the study by Feinstein, 140 MS patients were interviewed in an outpatient MS clinic in Toronto, Canada, for lifetime prevalence of DSM-IV major depression and anxiety disorders. He found that 40 patients (29%) had thought about committing suicide and 9 had attempted suicide. The patients with suicidal ideation had a similar demographic pattern and similar levels of neurological disability from MS but were much more likely to be actively depressed (30% vs 2% in the nonsuicidal group) or have a history of major depression in their lives (83% vs 18%). Risk factors for suicidal intent were the past or current depressive history, a family history of mental illness, living alone, and a history of alcohol abuse.

Two studies examined the potential effects of interferon-beta on depression in MS patients. In a large

trial, presented by Patten and Metz, of 365 patients with secondary progressive MS initiating interferon-beta1a at 2 doses (22 and 44 μ TIW), there was no significant difference in depression ratings before and after drug administration, and also no significant differences compared to the placebo group. Similarly, Feinstein et al studied 40 relapsing-remitting MS patients pre- and posttreatment with interferon-beta1b. At baseline, 21% of patients were diagnosed with a major depression, and these patients were started on antidepressant medication. There was an overall decrease in depression to 11% and 6% at months 6 and 12, respectively.

**COMMENTARY**

The high lifetime prevalence of depression in MS, 40-60% in most series, along with other variants of mood disorder including anxiety and bipolar-affective illness, should make the psychiatric complications of MS a central component of disease management. These studies provide an additional understanding of depression and suicidal behavior in patients with MS, documenting some predictable risk factors for suicidal ideation. Two studies reassuringly demonstrate that the use of interferon-beta does not significantly aggravate depression, particularly when used with antidepressant medication. Nonetheless, psychiatric complications, including depression and suicide, of the related type I interferon-alpha used at higher doses have been well described in the medical literature. Given the variable lifetime course for depression in MS, physicians should consistently probe for worsening mood complications of MS and treat aggressively with medication and/or mental health counseling. **—BRIAN R. APATOFF**

# Impaired Chemosensitivity to Hypoxia a Marker of Multiple System Atrophy

ABSTRACT & COMMENTARY

**Source:** Tsuda T, et al. Impaired chemosensitivity to hypoxia is a marker of multiple system atrophy. *Ann Neurol.* 2002;52: 367-371.

Multiple system atrophy (MSA) is a neurodegerative disorder that can take protean forms. Patients develop symptoms and signs in 1 or more of 3 neurologic systems: autonomic, cerebellar and parkinsonian. The major forms of MSA are Shy-Drager syndrome (autonomic failure), Olivo-Ponto-Cerebellar-Atrophy (cerebellar degeneration), and Striatonigral degeneration (parkinsonism that is usually poorly responsive to levodopa). These entities are united by a common pathologic feature, the presence of oligodendroglial cytoplasmic inclusions. During life it can be difficult to secure the diagnosis of MSA, particularly in older patients who present with pure cerebellar symptoms and signs. In this elegant paper, Tsuda and colleagues show that patients with the cerebellar form of MSA can be distinguished from idiopathic cerebellar degeneration before other signs of autonomic or parkinsonian disability develop.

Tsuda et al followed 9 control patients, 31 patients with idiopathic Parkinson's disease, 6 patients with Striatonigral degeneration, and 13 patients diagnosed with a sporadic cerebellar degeneration not linked to a trinucleotide repeat expansion. Of these 13 patients, 6 eventually developed parkinsonian and autonomic features consistent with MSA, and 7 did not. Chemosensitivity to hypoxia and hypercapnia were measured in each patient.

There was no difference in sensitivity to hypercapnia between any patient group and control. In contrast, the hypoxic ventilatory response was moderately depressed in patients with Parkinson's disease and severely depressed in those with Striatonigral degeneration. The 6 cerebellar patients who eventually developed other features of MSA had a profound depression in hypoxic ventilatory response even before parkinsonian and autonomic symptoms developed, while the 7 who remained with purely cerebellar signs did not.

**COMMENTARY**

Patients with MSA are at risk for sudden death for several reasons. They are prone to develop vocal cord abductor paresis, leading to nocturnal stridor. Stridor is a neurologic emergency, and once recognized should lead the astute clinician to intervene with nasal continuous positive airway pressure or even tracheostomy. However even patients who undergo tracheostomy can die from ventilatory failure. Tsuda et al's study offers a possible explanation for this problem. MSA patients have a profound impairment in chemosensivity to hypoxia. This is true even in those patients with the pure cerebellar form of the illness.

While tests of hypoxic ventilatory drive are not routinely available, this study suggests a useful approach to identify patients at risk for sudden death. It also implies that the neurodegenerative process in MSA affects neural systems important in ventilatory drive. **—STEVEN FRUCHT**

# Chemokines and CIDP

ABSTRACT & COMMENTARY

**Source:** Mahad DJ, et al. Expression of chemokines in cerebrospinal fluid and serum of patients with chronic inflammatory demyelinating polyneuropathy. *J Neurol Neurosurg Psychiatry.* 2002;73:320-323.

No single antigen has yet been identified as the target in all patients with chronic inflammatory demyelinating polyneuropathy (CIDP), a presumed autoimmune disorder similar to chronic experimental allergic neuritis, where both humoral and cell-mediated immune responses have been documented. Evidence suggests that specific chemokines play a role in pathogenesis.

Chemokines, cytokines that attract mononuclear cells to sites of inflammation, are divided into 4 families of which the majority are designated α and β chemokines, the former recruiting predominantly T lymphocytes, the latter T lymphocytes and monocytes. Serum and cerebrospinal fluid (CSF) levels were quantified in 9 CIDP patients, and compared to 10 benign headache and 10 nondemyelinating neuropathy (NDN) controls, to determine the presence of an association, if any, between CIDP and chemokines. α chemokines CXCL9 and CXCL10 and β chemokines CCL2, CCL3, and CCL5 were assayed using the ELISA method. Kruskal-Wallis and Mann-Whitney tests were used for statistical analysis.

CSF concentrations of CXCL9 and CXCL10 (α chemokines) were significantly elevated in CIDP patients ($P < 0.001$) compared to headache and NDN controls. CXCL9 was higher in serum than in CSF in 7 of 8 CIDP patients, and CXCL10 was higher in CSF than in serum in 6 of 9 CIDP patients. β chemokine CCL3, but not CCL2 or CCL5, was significantly elevated ($P = 0.043$) in the CIDP group compared to controls. CIDP patients with or without relapse or previous treatment did not demonstrate differential patterns of chemokine expression in the serum or CSF. Also, no correlation was found between chemokine levels and CSF protein. α chemokines CXCL9 and CXCL10 and β chemokine CCL3 may be involved in the pathogenesis of CIDP and may prove to be future targets in its treatment.

## COMMENTARY

Sural nerve biopsies from patients with Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (n = 10 each), and noninflammatory neuropathy controls (n = 8) were examined to determine the chemokine receptor expression pattern of their inflammatory infiltrates (*Brain.* 2002;125:823-834). Endoneurial macrophages expressed CCR-1 and CCR-5, while invading T lymphocytes expressed CCR-2, CCR-4 and CXCR-3. CXCR-3 was the receptor expressed in the highest numbers by invading T cells compared to other receptors. This suggeted that it might have a specific role in chemokine-mediated lymphocyte ingress into inflamed nerve. Using the Kruskal-Wallis and Mann-Whitney *U*-tests, interferon-γ-inducible protein (IP-10), a CXCR-3 ligand, was significantly increased ($P < 0.05$) in GBS and CIDP cerebrospinal fluid. *In situ* hybridization revealed that IP-10 mRNA was abundantly expressed in GBS inflamed perineurial vessels, probably in association with endothelial cells. Monokine induced by interferon-γ (Mig) did not differ among the patients and controls. Specific chemokine receptors and IP-10 appear to play a pathogenic role in inflammatory demyelinating neuropathy. **—MICHAEL RUBIN**

# New Treatments for Chorea in Huntington's Disease

ABSTRACT & COMMENTARY

**Source:** Metman LV, et al. A randomized, controlled trial using the NMDA-antagonist amantadine. *Neurol*. 2002;59:694-699.

Metman and associates carried out a controlled trial using amantadine to determine whether they could ameliorate chorea. This was based on prior studies showing that N-methyl-D-aspartate antagonists such as dextrophan, dextromethorphan, and amantadine can alleviate levodopa-induced chorea inpatients with parkinsonism. It has been suggested that NMDA receptor sensitization contributes to the production of choreiform movements. Metman et al conducted a randomized, placebo-controlled crossover study of 24 patients with HD for 2 weeks. Patients were initially treated with amantadine at 100 mg 4 times per day vs placebo for 2 weeks and then were crossed over to the opposite regimen. All 24 patients completed this study but 2 were unevaluable. Metman et al demonstrated that chorea scores were lower with amantadine as compared to placebo. The median reduction in extremity chorea

was 36% for the 22 evaluable patients and 56% in the 10 individuals with the highest plasma drug levels. Improvement correlated with plasma amantadine concentrations but did not correlate with the CAG repeat lengths of the patients. There was no worsening of parkinsonism scores. There was also no significant change in cognitive measures. There did not appear to be any significant adverse effects. Metman et al conclude that NMDA receptor supersenstivity contributes to choreiform dyskinesias in HD and that selective antagonists can confer palliative benefit.

### COMMENTARY

The development of an effective treatment for dyskinesias and chorea is a significant advance. Chorea in HD can usually be alleviated by drugs that inhibit dopaminergic neurotransmission. However, these drugs frequently cause untoward effects such as parkinsonism, akathisia, tardive dyskinesia, and sedation. The present results showing that amantadine significantly attenuates chorea in Huntington's Disease patients are consistent with Metman et al's prior results showing that amantadine attenuates dyskinesias in PD patients. They are also consistent with other studies showing that agents, which reduce glutamatergic neurotransmission significantly, attenuate hyperkinetic movements. For instance, we previously showed that riluzole significantly reduces choreic movements in HD patients. The NMDA receptor antagonist remacemide also has significant beneficial effects in animal models of PD.

Taken together, these observations implicate glutamatergic neurotransmission in the pathogenesis of hyperkinetic movement disorders. The evidence particularly implicates N-methyl-D-aspartate receptors, at which amantadine is a weak receptor antagonist.

The major question is whether this is a significant therapeutic advance. In early patients with predominant chorea, this well may be the case. In these patients, cognitive deficits and dystonia may be minimal. The social embarrassment of chorea may make treatment with amantadine extremely useful if it enables patients to resume a normal lifestyle for a few years (ie, the ability to go out in public without feeling socially ostracized). In the long run however, a treatment aimed solely at chorea is a temporary Band-Aid. The real cause of disability and inability of patients to function in either their jobs or social functions is cognitive dysfunction. This is most likely a consequence of neuronal degeneration in both frontal cortex and the basal ganglia. Until we have a treatment, which can effectively slow the neurodegenerative process, symptomatic treatment of chorea will remain a temporary solution. **—M. FLINT BEAL**

# Regional Atrophy Mapping: A Useful Window on Alzheimer's Disease

ABSTRACT & COMMENTARY

**Source:** Scahill RI, et al. Mapping the evolution of regional atrophy in Alzheimer's disease: Unbiased analysis of fluid-registered serial MRI. *Proc Natl Acad Sci U S A.* 2002;99:4703-4707.

SERIAL MRI MEASUREMENTS CAN BE USED TO MAP the pattern of regional brain atrophy in a variety of neurologic disease states. Using robust techniques that minimize the subjectivity of morphometric analysis, Scahill and colleagues compared rates and regional distribution of brain atrophy in 4 presymptomatic patients, 10 with mild Alzheimer's Disease (AD), 12 with moderate AD, and age-matched controls. They found that rates of atrophy varied across brain regions and across stages of the disease in a consistent way. Their findings advance our understanding of the pathophysiology of AD and may be useful for diagnosis as well as in the evaluation of potential disease modifying therapies.

Scahill et al obtained 2 T1-weighted 1.5T MRI scans from each subject at an interval of 1-2 years. They used a fluid registration model and the SPM99 image analysis program to determine the pattern and extent of regional brain atrophy within individuals and across groups over time. In presymptomatic cases that subsequently developed AD, volume loss was largely confined to the hippocampus and precuneous. By the mild stage of the disease, atrophy continued to occur in the hippocampus and precuneous but also involved the anterior frontal lobe, portions of the inferior and lateral temporal lobes, as well as the posterior cingulate region. In moderately affected AD patients, hippocampal atrophy rates were comparable to controls. Neocortical areas lost more volume in the moderate stages, including more extensive portions of the cortical regions described above.

Across AD subjects, slightly more atrophy was noted in the left hemisphere than the right. Areas of expanded volume included the lateral ventricles and the third ventricle. No significant atrophy was found in the cerebellum or primary sensorimotor areas.

### COMMENTARY

As postmortem studies have previously suggested, this study demonstrates that brain atrophy in living

AD procedes from the hippocampus and precuneous to the connected neocortical association areas. The hippocampus is devastated early in the disease and having been affected early on, it is relatively unchanged in the more severe stages of AD. The observation of slightly greater left than right-sided atrophy in AD is an interesting one that is not readily explained by existing theories of AD pathogenesis.

The areas of most profound atrophy on MRI correspond to those seen on functional imaging studies with PET of AD patients, even after corrections for brain atrophy are made. Quantitative PET studies are expensive, have lower spatial resolution, and can be technically challenging to perform. Serial MRI measurements use existing MRI scanners and are less expensive to perform, but do require specialized software and expertise for analysis. Is there a niche for the use of this technique in the clinical evaluation of dementia patients? Apart from future use in the evaluation of potential disease modifying therapies, serial atrophy measures may be useful in the evaluation of more challenging cases in which the differential diagnosis remains uncertain after conventional clinical and laboratory techniques are exhausted. **—NORMAN R. RELKIN**

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13. Publication Name: Neurology Alert — 14. Issue Date for Circulation Data Below: September 2002

| 15. Extent and Nature of Circulation | | | Average No. of Copies Each Issue During Preceding 12 Months | Actual No. Copies of Single Issue Published Nearest to Filing Date |
|---|---|---|---|---|
| a. Total No. Copies *(Net Press Run)* | | | 2232 | 2532 |
| b. Paid and/or Requested Circulation | (1) | Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)* | 1732 | 1761 |
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16. Publication of Statement of Ownership: Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 10/14/02

Donald R. Johnston

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PS Form **3526**, September 1999 *(Reverse)*

# CME Questions

**13. Each of the following causes of syncope is associated with an increased risk of premature death *except*:**
a. cardiogenic syncope.
b. neurogenic loss of consciousness (seizure).
c. syncope of unknown cause.
d. medication-induced hypotension.
e. TIAs.

**14. All of the following are potential risk factors for subarachnoid hemorrhage *except*:**
a. systolic hypertension.
b. cigarette smoking.
c. moderate alcohol intake.
d. more than 5 cups of coffee per day.

**15. The following chemokines may play a pathogenic role in chronic inflammatory demyelinating polyneuropathy:**
a. CXCL9, CXCL10, and CCL3.
b. CCL2, CCL3, and CCL5.
c. CXCL9, CXCL10, and CCL5.
d. CXCL9, CCL3, and CCL5.
e. CXCL10, CCL3, and CCL5.

## In Future Issues:

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November 1, 2002

Dear Readers:

We at *Neurology Alert* would like to take the time to thank you for your support in the last year. We, along with Drs. Fred Plum, Flint Beal, and the excellent team of physicians on our editorial advisory board, strive to bring you the best, most useful newsletter each month that we possibly can.

Over the last year, here are some of the special features we have included in *Neurology Alert*:

- www.neurologyalert.com. This web site offers a monthly survey of developments in neurologic medicine. Also featured are sections on Alzheimer's, Parkinsons, and MS.
- Late Breakers. This column offers short reviews of current therapeutics in both early and pivital stage development.
- *Pharmacology Watch*. This monthly supplement is a current update on the pharmaceutical industry and its effects on your daily practice. *Pharmacology Watch* is your source to the current events and announcements of the major pharmaceutical companies, as well as standings of ongoing trials, vaccines, and more.
- *Clinical Briefs in Primary Care*. This two-page supplement is included in every issue of *Neurology Alert*. It is the essential monthly primary care update.
- A cumulative, all-inclusive 2002 index.

As we approach 2003, you can look forward to 12 more issues of incisive, up-to-date commentary on developments in the field of neurology. We will continue to add "extras" that make your newsletter subscription an even greater value.

Our most important tool in keeping *Neurology Alert* relevant to your needs, as always, is the feedback that you give to us. Thank you to all who filled out and returned to us a reader survey or CME survey. This helps us a great deal. We'd like to hear about the issues that are important to you so that we can provide the most relevant information to help you, as a clinician, do a better job. Please direct your comments to Robert Kimball, Assistant Managing Editor, at robert.kimball@ahcpub.com, or call him directly at (404) 262-5413.

Thank you again for your support.

Sincerely,

The *Neurology Alert* Staff

# PHARMACOLOGY WATCH

## High-Dose Rofecoxib Confirmed Prothrombotic, Study Shows

Debate over the cardiovascular effects of COX-2 inhibitors has raged for more than a year since a special communication was published in *JAMA* last August (*JAMA*. 2001;286: 954-959) suggesting an increase in cardiovascular events with rofecoxib (Vioxx). As the argument goes, unlike nonselective NSAIDs, COX-2 inhibitors have no effect on thromboxane thus they do not inhibit platelet aggregation. However they do inhibit vascular prostacyclin—an effect that may be prothrombotic. Nonselective NSAIDs inhibit both thromboxane and prostacyclin. Whether COX-2 inhibitors are prothrombotic or merely lack the antiplatelet action of nonselective NSAIDs is at the crux of the debate. Now a large retrospect, the cohort study from the Tennessee Medicaid program seems to confirm the prothrombotic effects of rofecoxib, at least in high dose. Researchers from Vanderbilt University reviewed the records of 202,916 patients who did not use anti-inflammatories, 151,728 patients who used "other" anti-inflammatories, and 24,132 patients on rofecoxib over the 18 months between January 1999 and June 2001. Participants were between 50 and 84 years of age and had no life-threatening noncardiovascular illnesses. Users of high-dose rofecoxib (50 mg/d) were 1.7 times more likely than nonusers to have serious CHD (95% CI, 0.98-2.95; $P = 0.058$). Among new users of high dose rofecoxib, the rate increased to 1.93 (1.09-3.42, $P = 0.058$). There was, however, no increase risk of CHD with lower doses of rofecoxib or with use of other NSAIDs (*Lancet*. 2002;360:1071-1073). This study supports the hypothesis that high-dose COX-2 inhibition may be prothrombotic. This evidence is supported by a study in genetically engineered mice. Mice that lack the prostacyclin receptor (a defect that is similar to the effects of COX-2 inhibitors) overproduce thromboxane A2—and are likely to form arterial clots (*Science*. 2002;296:539-541). A recent "Clinical Implications of Basic Research" elegantly depicts the eicosanoid balance and the effects of these drugs on clotting (*N Engl J Med*. 2002;347:1025-1026).

### *Losartan Better Than Atenolol for LVH Treatment*

Losartan is a better option than atenolol for treating isolated systolic hypertension in patients with left ventricular hypertrophy according to a new study. More than 1300 men and women with systolic hypertension and ECG evidence of LVH were randomized to treatment with losartan or atenolol with hydrochlorothiazide added as a second agent as needed. The main outcome measure was a composite end point of cardiovascular death, stroke, or myocardial infarction. After a mean of 4.7 years of follow-up, the main outcome was reduced by 25% with losartan compared with atenolol. There were 25.1 events per 1000 patients years in the losartan group vs. 35.4 in the atenolol group (relative risk [RR] 0.75; 95% confidence interval, 0.56-1.01; $P = 0.6$). There was no difference in the rate of myocardial infarction; however, cardiovascular mortality was significantly decreased in the losartan group as was nonfatal and fatal stroke. Total mortality was also significantly lower than the losartan group (21.2 vs 30.2 events per thousand patient-years; RR, 0.72; 95% CI, 0.53-1.00; $P = .046$). New onset diabetes was also significantly reduced in

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the losartan group, a finding that has been seen in other studies of ARBs. Losartan was also better tolerated than atenolol (*JAMA*. 2002;288:1491-1498).

### Lisinopril, Not Losartan, Improves Myocardial Perfusion

In a related study of patients with hypertension and LVH, long-term treatment with lisinopril but not losartan improved myocardial perfusion in maximal coronary blood flow. In this small study, 17 patients with hypertension and LVH (9 treated with lisinopril, 8 treated with losartan) were evaluated with positron emission tomography at baseline and after coronary vasodilation with dipyridamole. The same studies were done on 8 normotensive control patients. After treating with lisinopril, maximal coronary blood flow and myocardial perfusion reserve increased significantly compared with pretreatment values ($P = 0.02$, and $P = 0.002$ respectively). Post-treatment hyperemic flow in patients treated with lisinopril was not significantly different from corresponding measurements and control patients. No difference in either measure was noted with losartan. The authors postulate that angiotensin converting enzyme inhibitors potentiate endogenous bradykinins, which in turn improve myocardial perfusion reserve. Losartan, like other angiotensin receptor blockers, has no effect on bradykinins, which may explain the lack of improvement in this measure. The authors postulate that ACE inhibitors may be more effective in repairing the coronary microangiopathy associated with hypertension-induced LVH (*J Am Coll Cardiol*. 2002;40:703-709).

### New Fluoroquinolone Study

It seems that every year there is a new study linking antibiotic use with a reduction in coronary disease. The most recent is a Dutch study of Type 2 diabetics. Using a national hospitalization database from 8 cities, researchers found a significantly reduced risk of CHD in patients who had used at least 14 days of a fluoroquinolone in the 3-year study period (odds ratio = .30; 95% CI, 0.12-0.75). No other antibiotic was associated with a reduction in CHD including tetracyclines, macrolides, cephalosporins, or penicillin derivatives (*Eur Heart J*. 2002;23:1575-1579). And while the explanation for such improvement is still elusive, ongoing research is looking into the CHD/inflammation/infection connection.

### Warfarin After MI Better Than Aspirin Alone

Warfarin, with or without aspirin, is better than aspirin alone in preventing vascular events after myocardial infarction according to a new study. In a randomized, multicenter trial, 1216 patients received warfarin (target INR 2.8 to 4.2), 1206 received aspirin 160 mg per day, and 1208 received aspirin 75 mg per day combined with warfarin (target INR 2.0 to 2.6). The mean duration of the study was 4 years and the primary outcome was a composite of death, nonfatal reinfarction, or thromboembolic cerebral stroke. The results showed a recurrence rate of 20% in the aspirin group (241 of 1206), 16.7% in the warfarin group (203 of 1216), and 15% in the combined warfarin in aspirin group (181 of 1208). The difference between the warfarin and warfarin/aspirin group was not statistically significant. There was a statistically significant increase in major, nonfatal bleeding in both warfarin groups compared to the aspirin group (0.62% vs 0.17%, respectively [$P < 0.001$]). The authors conclude that warfarin given alone or in combination with aspirin is superior to aspirin alone in reducing the incidence of composite vascular end points after myocardial infarction; however warfarin therapy is associated with a higher risk of bleeding. No difference in mortality was noted between the 2 groups (*N Engl J Med*. 2002; 347:969-974).

### FDA News

Valacyclovir (Valtrex-GlaxoSmithKline) has been approved for the treatment of cold sores (herpes labialis). The approval was based on to studies that showed that valacyclovir 2 g twice a day for 1 day shortens the duration of cold sore outbreaks by about 1 day.

The FDA is one step closer two approving tiotropium (Spiriva-Boehringer Ingelheim), a new long-acting anticholinergic agent for the treatment of COPD. The drug was reviewed by the FDA's Pulmonary Allergy Drugs Advisory Committee and endorsed for the treatment of bronchospasm, however there was no support for the proposed indication of dyspnea.

The agency has strengthened its warnings on mefloquine (Larium-Roche) because of concerns of CNS side effects. Mefloquine is used in the treatment and prevention of malaria. The FDA specifically stated that mefloquine is contraindicated in patients with psychiatric disorders including active depression, recent history depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders, or with a history of convulsions. The FDA also warns that patients taking the drug for prophylaxis should discontinue it immediately if psychiatric symptoms should develop. Roche has recently issued a "Dear Dr. letter" regarding these warnings. ■